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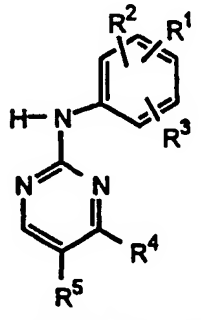
(54) Title: 4,5-DISUBSTITUTED-2-AMINOPYRIMIDINES



(1)

(57) Abstract: Pyrimidines of formula (1) are described, wherein R^1 is a $-XR^6$ group; R^2 and R^3 which may be the same or different is each a hydrogen or halogen atom or a group selected from an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, -OH, $-OR^{10}$ [where R^{10} is an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group] -SH, $-NO_2$, -CN, $-SR^{10}$, $-COR^{10}$, $S(O)R^{10}$, $-SO_2R^8$, $-SO_2N(R^8)(R^9)$, $-CO_2R^8$, $-CON(R^8)(R^9)$, $-CSN(R^8)(R^9)$, $-NH_2$ or substituted amino group; R^4 is a X^1R^{11} group where X^1 is a covalent bond or a $-C(R^{12})(R^{13})$-[where each of R^{12} and R^{13} is a hydrogen or halogen atom or a hydroxyl, alkyl or haloalkyl group] or -C(O)- group and R^{11} is an optionally substituted phenyl, thienyl, thiazolyl or indolyl group; R^5 is a halogen atom or an alkynyl group; and the salts, solvates, hydrates and N-oxides thereof. The compounds are selective KDR kinase and/or FGFr kinase inhibitors and are of use in the prophylaxis and treatment of disease states associated with angiogenesis.

4,5-DISUBSTITUTED-2-AMINOPYRIMIDINES

This invention relates to certain 4,5-disubstituted-2-aminopyrimidines, to processes for their preparation, to pharmaceutical compositions containing them, and to their use in medicine.

Angiogenesis, the growth of capillaries from existing blood vessels, is an essential process in normal embryonic development, tissue repair and some aspects of female reproductive function. It is also associated with the development of several pathological disorders including solid tumour growth, metastasis, psoriasis and rheumatoid arthritis, as well as diabetic retinopathy and age related macular degeneration (Folkman, Nature Medicine, (1995) 1, 27-310).

Several growth factors have been shown to mediate angiogenesis through alteration of vascular permeability, including vascular endothelial growth factor (VEGF; G. Breier *et al.*, Trends in Cell Biology, 1996, 6, 454-6), platelet derived growth factor (PDGF) and acidic and basic fibroblast growth factors (a & b FGF).

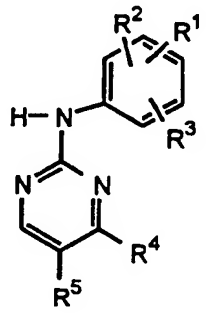
VEGF in dimeric form is a ligand that binds to two transmembrane tyrosine kinase associated receptors, expressed exclusively on proliferating endothelial cells, KDR (Flk-1 in mice) also known as VEGFR-2, and Flt-1 also known as VEGFR-1. Binding of VEGF to KDR/Flk and Flt leads to receptor dimerisation, kinase activation, autophosphorylation of the receptor and phosphorylation of intracellular substrates. An analogous series of events ensues after ligand occupancy of the more widely expressed tyrosine kinase associated FGFr receptor by aFGF or bFGF. Thus receptor tyrosine kinase activity initiates a cellular signalling pathway leading to proliferation.

Antagonism of VEGF with antibody completely suppresses neovascularisation and growth of human rhabdomyosarcoma A673 speroids in athymic mice (Borgstrom *et al*, Cancer Res., 1996, 56 4032-4039). Suppression of bFGF gene expression by interferons α and β

inhibits capillary density in mice, leading to pancreatic eyelet tumour suppression (Folkman *et al*, Proc. Natl. Acad.Sci. 1996, 93, 2002 and Singh *et al* Proc.Natl. Acad. Sci. 1995, 92, 10457). Other receptor associated kinases such as PDGFβ and EGFr may also have some role in mediating angiogenesis.

We have now found certain 4,5-disubstituted-2-aminopyrimidines which are potent and selective inhibitors of receptor tyrosine kinases involved in angiogenesis, especially KDR kinase and/or FGFr kinase. Selective inhibition of these kinases can be expected to have a beneficial effect and the compounds are thus of use in the prophylaxis and treatment of disease states associated with angiogenesis, as described hereinafter.

Thus, according to one aspect of the invention, we provide a compound of formula (1):



(1)

wherein R^1 is a $-XR^6$ group [where X is a covalent bond, -O-, -S-, -C(O)-, -C(S)-, -C(O)O-, -S(O)-, $-S(O_2)-$, $-CH_2-$, -or $N(R^7)-$ [where R^7 is a hydrogen atom or a straight or branched alkyl group] and R^6 is a hydrogen or halogen atom or an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group, or a $-NO_2$, -CN, $-SO_2N(R^8)(R^9)$ [where R^8 and R^9, which may be the same or different is a hydrogen atom or an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group], $-CON(R^8)(R^9)$, $-CSN(R^8)(R^9)$, $-NH_2$ or substituted amino group;

R^2 and R^3 which may be the same or different is each a hydrogen or halogen atom or a group selected from an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, -OH, -OR^{10} [where R^{10} is an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group] -SH, -NO_2, -CN, -SR^{10}, -COR^{10}, $S(O)R^{10}$, -SO_2R^8, -$SO_2N(R^8)(R^9)$, -CO_2R^8, -$CON(R^8)(R^9)$, -$CSN(R^8)(R^9)$, -NH_2 or substituted amino group;
R^4 is a X^1R^{11} group where X^1 is a covalent bond or a -$C(R^{12})(R^{13})$- [where each of R^{12} and R^{13} is a hydrogen or halogen atom or a hydroxyl, alkyl or haloalkyl group] or -C(O)- group and R^{11} is an optionally substituted phenyl, thienyl, thiazolyl or indolyl group;
R^5 is a halogen atom or an alkynyl group;
and the salts, solvates, hydrates and N-oxides thereof.

In the compounds of formula (1), the term "optionally substituted aliphatic group" when applied to each of the groups R^2, R^3, R^6 and R^{10} means each of these groups may independently be for example an optionally substituted C_{1-10} aliphatic group, for example an optionally substituted straight or branched chain C_{1-6} alkyl, e.g. C_{1-3} alkyl, C_{2-6} alkenyl, e.g. C_{2-4} alkenyl, or C_{2-6} alkynyl, e.g. C_{2-4} alkynyl group. Each of said groups may be optionally interrupted by one or two heteroatoms or heteroatom-containing groups represented by X^2 [where X^2 is an -O- or -S- atom or a -C(O)-, -C(S)-, -S(O)-, -$S(O)_2$-, -$N(R^{14})$- [where R^{14} is a hydrogen atom or a C_{1-6} alkyl, e.g. methyl or ethyl, group], -$CON(R^{14})$-, -$OC(O)N(R^{14})$-, -$CSN(R^{14})$-, -$N(R^{14})CO$-, -$N(R^{14})C(O)O$-, -$N(R^{14})CS$-, -$SON(R^{14})$, -$SO_2N(R^{14})$, -$N(R^{14})SO_2$-, -$N(R^{14})CON(R^{14})$-, -$N(R^{14})CSN(R^{14})$-, -$N(R^{14})SON(R^{14})$- or -$N(R^{14})SO_2N(R^{14})$ group] to form an optionally substituted R^2, R^3, R^6 and R^{10} heteroaliphatic group.

Particular examples of aliphatic groups represented by R^2, R^3, R^6 and/or R^{10} include optionally substituted -CH_3, -CH_2CH_3, -$(CH_2)_2CH_3$, -$CH(CH_3)_2$, -$(CH_2)_3CH_3$, -$CH(CH_3)CH_2CH_3$, -$CH_2CH(CH_3)_2$, -$C(CH_3)_3$, -$(CH_2)_4CH_3$, -$(CH_2)_5CH_3$, -$CHCH_2$, -$CHCHCH_3$, -CH_2CHCH_2, -$CHCHCH_2CH_3$, -$CH_2CHCHCH_3$, -$(CH_2)_2CHCH_2$, -CCH, -$CCCH_3$, -CH_2CCH, -$CCCH_2CH_3$, -CH_2CCCH_3, or -$(CH_2)_2CCH$ groups. Where appropriate each of said groups may be optionally interrupted by one or

two atoms and/or groups X^2 to form an optionally substituted heteroaliphatic group. Particular examples include $-CH_2X^2CH_3$, $-CH_2X^2CH_2CH_3$, $-(CH_2)_2X^2CH_3$ and $-(CH_2)_2X^2CH_2CH_3$ groups.

The optional substituents which may be present on these aliphatic and/or heteroaliphatic groups include one, two, three or more substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl, C_{1-6} alkoxy, e.g. methoxy or ethoxy, thiol, C_{1-6} alkylthio e.g. methylthio or ethylthio, $-SC(NH)NH_2$, $-CH_2C(NH)NH_2$, amino, substituted amino, cyclic amino or heteroaromatic groups.

Substituted amino groups include for example groups of formulae $-NR^{15}R^{16}$ [where R^{15} is an optionally substituted C_{1-6} alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl group optionally interrupted by one or two heteroatoms or heteroatom-containing groups represented by X^3 (where X^3 is an atom or group as described above for X^2) and R^{16} is a hydrogen atom or is a group as just defined for R^{15}], $-N(R^{16})COR^{15}$, $-N(R^{16})CSR^{15}$, $-N(R^{16})SOR^{15}$, $-N(R^{16})SO_2R^{15}$, $-N(R^{16})CONH_2$, $-N(R^{16})CONR^{15}R^{16}$, $-N(R^{16})C(O)OR^{15}$, $-N(R^{16})C(NH)NH_2$, $-N(R^{16})C(NH)NR^{15}R^{16}$, $-N(R^{16})CSNH_2$, $-N(R^{16})CSNR^{15}R^{16}$, $-N(R^{16})SONH_2$, $-N(R^{16})SONR^{15}R^{16}$, $-N(R^{16})SO_2NH_2$, $-N(R^{16})SO_2NR^{15}R^{16}$, or $-N(R^{16})Cyc^1$ [where Cyc^1 is an optionally substituted C_{3-7} monocyclic carbocyclic group optionally containing one or more -O- or -S- atoms or $-N(R^{14})-$, -C(O)-, -C(S)-. -S(O)- or $-S(O_2)-$ groups].

Cyclic amino substituents which may be present on R^2, R^3, R^6 and/or R^{10} aliphatic or heteroaliphatic groups include groups of formula $-NHet^1$, where $-NHet^1$ is an optionally substituted C_{3-7} cyclic amino group optionally containing one or more other heteroatoms or heteroatom containing groups selected from -O- or -S- atoms $-N(R^{14})-$, -C(O), -C(S)-, -S(O)- or $-S(O_2)-$ groups.

Particular examples of amino, substituted amino and cyclic amino groups include $-NH_2$, methylamino, thylamino, dimethylamino, diethylamino, $-NHCyc^1$ where Cyc^1 is an optionally substituted cyclop ntyl, cyclohexyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, morpholinyl,

piperazinyl or thiomorpholinyl group, or -NH t^1 wh r -NHet^1 is an optionally substituted pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, morpholinyl, piperazinyl or thiomorpholinyl group. Optional substituents which may be present on these groups and substituted and cyclic amino groups in general include one, two or three halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C_{1-4}alkyl, e.g. methyl or ethyl, hydroxyl, C_{1-4}alkoxy, e.g. methoxy or ethoxy or pyridyl groups.

Optional heteroaromatic substituents which may be present on the aliphatic or heteroaliphatic groups represented by R^2, R^3, R^6 and/or R^{10} include those heteroaromatic groups described below in relation to R^2, R^3, R^6 and R^{10}.

When R^2, R^3, R^6 and/or R^{10} is present in compounds of formula (1) as an optionally substituted cycloaliphatic group it may be an optionally substituted C_{3-10} cycloaliphatic group. Particular examples include optionally substituted C_{3-10}cycloalkyl, e.g. C_{3-7}cycloalkyl, or C_{3-10}cycloalkenyl e.g. C_{3-7}cycloalkenyl groups.

Heteroaliphatic or heterocycloaliphatic groups represented by R^2, R^3, R^6 and/or R^{10} include the aliphatic or cycloaliphatic groups just described for these substituents but with each group additionally containing one, two, three or four heteroatoms or heteroatom-containing groups represented by X^2, where X^2 is as described above.

Particular examples of R^2, R^3, R^6 and/or R^{10} cycloaliphatic and heterocycloaliphatic groups include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2,4-cyclopentadien-1-yl, 3,5,-cyclohexadien-1-yl, tetrahydrofuranyl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4- oxazinyl, 1,2,5-oxathiazinyl,

isoxazinyl, oxathiazinyl, .g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5-oxadiazinyl groups.

Optional substituents which may be present on R^2, R^3, R^6 and/or R^{10} cycloaliphatic and heterocycloaliphatic groups include those optional substituents described above for R^6 when it is an aliphatic group. The heterocycloaliphatic groups may be attached to the remainder of the molecule of formula (1) through any appropriate ring carbon or heteroatom.

When R^2, R^3, R^6 and/or R^{10} is present as an aromatic group in compounds of formula (1) it may be for example an optionally substituted monocyclic or bicyclic fused ring C_{6-12} aromatic group, such as an optionally substituted phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl group.

Heteroaromatic groups represented by R^2, R^3, R^6 and/or R^{10} include optionally substituted C_{1-9} heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example nine- to thirteen-membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Examples of heteroaromatic groups represented by R^2, R^3, R^6 and/or R^{10} include optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, N-methylimidazolyl, N-ethyl-imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, isobenzothienyl, indolyl, isoindolyl,

benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, and imidyl, e.g. succinimidyl, phthalimidyl, or naphthalimidyl such as 1,8-naphthalimidyl.

Optional substituents which may be present on any of the just described aromatic or heteroaromatic groups include one, two, three or more substituents, each represented by the group R^{17} as more particularly defined below in relation to the phenyl substituent R^{11}.

Substituted amino groups represented by the groups R^1, R^2 and/or R^3 in compounds of formula (1)include for example the groups $-NR^{15}R^{16}$, $-N(R^{16})COR^{15}$, $-N(R^{16})CSR^{15}$, $-N(R^{16})SOR^{15}$, $-N(R^{16})SO_2R^{15}$, $-N(R^{16})CONH_2$, $-N(R^{16})CONR^{15}R^{16}$, $-N(R^{16})C(O)OR^{15}$, $-N(R^{16})C(NH)NH_2$, $-N(R^{16})C(NH)NR^{15}R^{16}$, $-N(R^{16})CSNH_2$, $-N(R^{16})CSNR^{15}R^{16}$, $-N(R^{16})SONH_2$, $-N(R^{16})SONR^{15}R^{16}$, $-N(R^{16})SO_2NH_2$, $-N(R^{16})SO_2NR^{15}R^{16}$, $-N(R^{16})Cyc^1$ where R^{15}, R^{16} and Cyc^1 are as defined above.

Halogen atoms represented by the group R^5 in compounds of the invention include fluorine, chlorine, bromine and iodine atoms. Alkynyl groups represented by R^5 include -CCH and $CCCH_3$ groups.

The group R^{11} in compounds of formula (1) may be a phenyl or substituted phenyl group. The substituted phenyl group may contain one, two, three or more substituents, each represented by the group R^{17}.

The substituent R^{17} may be selected from an atom or group R^{18} or $-Alk(R^{18})_m$, where R^{18} is a halogen atom, or an amino ($-NH_2$), $-NHR^{19}$ [where R^{19} is an $-Alk(R^{18})_m$, heterocycloaliphatic, -Alk-heterocycloaliphatic, aryl or heteroaryl group], $-N(R^{19})_2$ [where each R^{19} group is the same or different], nitro, cyano, hydroxyl (-OH), $-OR^{19}$, formyl, carboxyl ($-CO_2H$), esterified carboxyl, thiol (-SH), $-SR^{19}$, $-COR^{19}$, $-CSR^{19}$, $-SO_3H$, $-SO_2R^{19}$, $-SO_2NH_2$, $-SO_2NHR^{19}$, $SO_2N[R^{19}]_2$, $-CONH_2$, $-CSNH_2$,

-$CONHR^{19}$, -$CSNHR^{19}$, -$CON[R^{19}]_2$, -$CSN[R^{19}]_2$, -$N(R^{14})SO_2H$ [wher R^{14} is as defined above], -$N(R^{14})SO_2R^{19}$, -$N[SO_2R^{19}]_2$, -$N(R^{14})SO_2NH_2$, -$N(R^{14})SO_2NHR^{19}$, -$N(R^{14})SO_2N[R^{19}]_2$, -$N(R^{14})COR^{19}$, -$N(R^{14})CONH_2$, -$N(R^{14})CONHR^{19}$, -$N(R^{14})CON[R^{19}]_2$, -$N(R^{14})CSR^{19}$, -$N(R^{14})CSNH_2$, -$N(R^{14})CSNHR^{19}$, -$N(R^{14})CSN[R^{19}]_2$, -$N(R^{14})C(O)OR^{19}$, or an optionally substituted cycloaliphatic, heterocycloaliphatic, aryl or heteroaryl group; Alk is a straight or branched C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms or S(O)-, -$S(O)_2$- or -$N(R^{14})$- groups; and m is zero or an integer 1, 2 or 3.

When in the group -$Alk(R^{18})_m$ m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{18} may be present on any suitable carbon atom in -Alk. Where more than one R^{18} substituent is present these may be the same or different and may be present on the same or different atom in -Alk or in R^{17} as appropriate. Thus for example, R^{17} may represent a -$CH(R^{18})_2$ group, such as a -CH(OH)Ar group where Ar is an aryl or heteroaryl group as defined below. Clearly, when m is zero and no substituent R^{18} is present the alkylene, alkenylene or alkynylene chain represented by Alk becomes an alkyl, alkenyl or alkynyl group.

When R^{18} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

Esterified carboxyl groups represented by the group R^{18} include groups of formula -CO_2Alk^1 wherein Alk^1 is a straight or branched, optionally substituted C_{1-8} alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C_{6-12}arylC_{1-8}alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthyl-methyl or 2-naphthylmethyl group; a C_{6-12}aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C_{6-12}aryloxyC_{1-8}alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; an optionally substituted C_{1-8}alkanoyloxyC_{1-8}alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C_{6-12}aroyloxyC_{1-8}alkyl group such as an optionally substituted benzoyloxy thyl or benzoyl-

oxypropyl group. Optional substituents present on the Alk^1 group include R^{18} substituents described above.

When Alk is present in or as a substituent R^{17} it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, $-S(O)_2-$ or $-N(R^{14})-$ groups.

When R^{18} is present in compounds of formula (1) as an optionally substituted cycloaliphatic group it may be an optionally substituted C_{3-10} cycloaliphatic group. Particular examples include optionally substituted C_{3-10}cycloalkyl, e.g. C_{3-7}cycloalkyl, or C_{3-10}cycloalkenyl e.g. C_{3-7}cycloalkenyl groups.

Heterocycloaliphatic groups represented by R^{19} and when present R^{19} include the cycloaliphatic groups just described for R^{18} but with each group additionally containing one, two, three or four heteroatoms or heteroatom-containing groups selected from -O- or -S- atoms or $-N(R^{14})-$, -C(O), -C(S)-, -S(O)- or $-S(O_2)-$ groups.

Particular examples of R^{18} cycloaliphatic and R^{18} or R^{19} heterocycloaliphatic groups include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2,4-cyclopentadien-1-yl, 3,5,-cyclohexadien-1-yl, tetrahydrofuranyl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4- oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5-oxadiazinyl groups.

Optional substituents which may be present on R^{18} cycloaliphatic and R^{18} or R^{19} heterocycloaliphatic groups include one, two, three or more

substituents selected from halogen atoms, .g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl, C_{1-6}alkoxy, e.g. methoxy or ethoxy, thiol, C_{1-6}alkylthio, e.g. methylthio or ethylthio, hydroxy, C_{1-6}alkyl, e.g. hydroxymethyl, hydroxyethyl, -CN, $-NO_2$, $-NHR^{14}$ or $-N(R^{14})_2$ groups.

Aryl and heteroaryl groups represented by the group R^{18} or Ar include for example optionally substituted monocyclic or bicyclic C_{6-12} aromatic groups, e.g. phenyl groups, or C_{1-9} heteroaromatic groups such as those described above in relation to the group R^6. Optional substituents which may be present on these groups include one, two or three R^{18a} atoms or groups described below.

Particularly useful atoms or groups represented by R^{18}, $-Alk(R^{18})_m$ or R^{18a} as appropriate include fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl or ethyl, C_{1-6}alkylamino, e.g. methylamino or ethylamino, C_{1-6}hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, C_{1-6}alkylthiol e.g. methylthiol or ethylthiol, C_{1-6}alkoxy, e.g. methoxy or ethoxy, C_{5-7}cycloalkoxy, e.g. cyclopentyloxy, haloC_{1-6}alkyl, e.g. trifluoromethyl, C_{1-6}alkylamino, e.g. methylamino or ethylamino, amino ($-NH_2$), aminoC_{1-6}alkyl, e.g. aminomethyl or aminoethyl, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, 1,1,3-trioxo-benzo[d]-thiazolidino, nitro, cyano, hydroxyl (-OH), formyl [HC(O)-], carboxyl ($-CO_2H$), $-CO_2Alk^1$ [where Alk^1 is as defined above], C_{1-6} alkanoyl e.g. acetyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl or thioethyl, $-SC(NH_2+)NH_2$, sulphonyl ($-SO_3H$), C_{1-6}alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl ($-SO_2NH_2$), C_{1-6}alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6}dialkylaminosulphonyl, e.g. dimethylamino-sulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido ($-CONH_2$), C_{1-6}alkylaminocarbonyl, e.g. methylaminocarbonyl or ethyl-aminocarbonyl, C_{1-6}dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, sulphonylamino ($-NHSO_2H$), C_{1-6}alkylsulphonyl-amino, e.g. methylsulphonylamino or ethylsulphonylamino, C_{1-6}dialkyl-sulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, e.g. 2-, 3- or 4- substituted phenylsulphonylamino such as 2-nitrophenylsulphonylamin , amino-

sulphonylamino ($-NHSO_2NH_2$), C_{1-6}alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C_{1-6}dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, phenylaminosulphonylamino, aminocarbonylamino, C_{1-6}alkylaminocarbonylamino e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C_{1-6}dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, phenylaminocarbonylamino, C_{1-6}alkanoylamino, e.g. acetylamino, optionally substituted phenylcarbonylamino, C_{1-6}alkanoylaminoC_{1-6}alkyl, e.g. acetylaminomethyl, C_{1-6} alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino, optionally substituted heteroC_{3-6}cycloalkyl, e.g. piperidinyl, piperazinyl, 4-(C_{1-6}alkyl)piperazinyl, e.g. 4-methylpiperazinyl, homopipeprazinyl, or morpholinyl, optionally substituted heteroC_{3-6}cycloalkylC_{1-6}alkyl, e.g. piperidinylC_{1-6}alkyl, piperazinylC_{1-6}alkyl, 4-(C_{1-6}alkyl)piperazinylC_{1-6}alkyl, e.g. 4-methylpiperazinylmethyl, or morpholinyl-C_{1-6}alkyl, optionally substituted heteroC_{3-6}alkylC_{1-6}alkylamino, optionally substituted heteroC_{3-6}cycloalkylamino, tetrazolyl, optionally substituted imidazolylC_{1-6}alkyl, optionally substituted phenylamino, optionally substituted benzylamino, optionally substituted benzyloxy, or optionally substituted pyridylmethylamino group.

Where desired, two R^{18} or $-Alk(R^{18})_m$ or R^{18a} substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{2-6}alkylenedioxy group such as ethylenedioxy.

It will be appreciated that where two or more R^{18}, $-Alk(R^{18})_m$ or R^{18a} substituents are present, these need not necessarily be the same atoms and/or groups.

Especially useful R^{18}, $-Alk(R^{18})_m$ or R^{18a} substituents include for example fluorine, chlorine, bromine or iodine atoms, or a methylamino, ethylamino, hydroxymethyl, hydroxyethyl, methylthiol, ethylthiol, methoxy, ethoxy, n-propoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 4-hydroxybutoxy, 2-aminoethoxy, 3-aminopropoxy, 2-(methylamino)ethoxy, 2-(dimethylamino)ethoxy, 3-(dimethylamino)propoxy, cyclopentyloxy, cyclohexyl, cyclohexylamino, 2-hydroxycyclohexylamino, trifluoromethyl, trifluoromethoxy, methylamino,

ethylamino, amino ($-NH)_2$, aminomethyl, aminoethyl, dimethylamino, diethylamino, ethyl(methyl)amino, propyl(methyl)amino, 2-hydroxyethylamino, 3-hydroxypropylamino, 4-hydroxybutylamino, 2-aminoethylamino, 3-aminopropylamino, 4-aminobutylamino, 2-(methylamino)ethylamino, 2-(ethylamino)ethylamino, 2-(i-propylamino)ethylamino, 3-(i-propylamino)propylamino, 2-(dimethylamino)ethylamino, 3-(dimethylamino)propylamino, 2-(diethylamino)ethylamino, 3-(diethylamino)propylamino, 2-(methylamino)ethyl(methyl)amino, 3-(methylamino)propyl(methyl)amino, 2-(dimethylamino)ethyl(methyl)amino, 2-(dimethylamino)ethyl(ethyl)amino, nitro, cyano, hydroxyl (-OH), formyl [HC(O)-], carboxyl ($-CO_2H$), $-CH_2CO_2H$, $-OCH_2CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, $-CH_2CO_2CH_2$phenyl, t-butoxycarbonylmethoxy, acetyl, phenacetyl, thio (-SH), thiomethyl, thioethyl, $-SC(NH)NH_2$, sulphonyl ($-SO_2H$), methylsulphonyl, methylaminosulphonyl, ethylaminosulphonyl, dimethylaminosulphonyl, diethylaminosulphonyl, carboxamido ($-CONH_2$), methylaminocarbonyl, ethylaminocarbonyl, dimethylaminocarbonyl, diethylaminocarbonyl, methylaminocarbonylmethyl, $-NHC(S)NH_2$, sulphonylamino ($-NHSO_2H$), methylsulphonylamino ethylsulphonylamino, dimethylsulphonylamino, diethylsulphonylamino, sulphonylamino ($-NHSO_2NH_2$), methylaminosulphonylamino, ethylaminosulphonylamino, dimethylaminosulphonylamino, diethylaminosulphonylamino, methylaminocarbonylamino, ethylaminocarbonylamino, dimethylaminocarbonylamino diethylaminocarbonylamino, acetylamino, phenylcarbonylamino, aminomethylcarbonylamino, acetylaminomethyl, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, pyrrolidinyl, piperidinyl, piperazinyl, 4-methylpiperazinyl, homopiperazinyl, morpholinyl, pyrrolidinylC_{1-6}alkyl, piperidinylC_{1-6}alkyl, piperazinylC_{1-6}alkyl, 4-(C_{1-6}alkyl)piperazinylC_{1-6}akyl, morpholinylC_{1-6}alkyl, 2-pyrrolidinylethylamino, 2-(1-methylpyrrolidinyl)ethylamino, 1-ethylpyrrolidinylmethylamino, piperidinylamino, 1-benzylpiperidinylamino, imidazolylmethyl, imidazolylethyl, 4-(methoxy)phenylamino, 4-(3-hydroxypropyl)phenylamino, benzylamino, benzyloxy or pyridiylmethylamino group.

When X^1 is present in compounds of the invention as a $-(R^{12})(R^{13})-$ group it may be for example a $-CH_2-$ or $-C(R^{12})(R^{13})-$ group in which R^{12} and/or R^{13} is each a halogen atom such as a fluorine or chlorine atom or a

hydroxy, C_{1-6}alkyl e.g. methyl, thyl or i-propyl, or C_{1-6}haloalkyl, e.g. trihalomethyl such as a trifluoromethyl group. Particular examples of such $-C(R^{12})(R^{13})-$ groups include -CHF-, $-CH(CH_3)-$, $-C(OH)(CF_3)-$ and $-CH(CF_3)-$ groups.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isethionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, piperazine, dimethylamine or diethylamine salts.

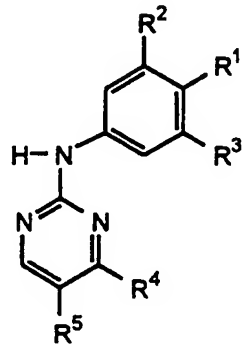
Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

It will be appreciated that depending on the nature of the substituents R^1, R^2, R^3 and R^4 the compounds of formula (1) may exist as tautomers and/or geometrical isomers and/or may have one or more chiral centres so that enantiomers or diasteromers may exist. It is to be understood that the invention extends to all such tautomers and isomers of the compounds of formula (1), and to mixtures thereof, including racemates.

In the compounds according to the invention the group R^4 is preferably a group X^1R^{11} in which X^1 is a covalent bond.

The group R^5 in compounds of the invention is in particular a bromine or, especially a chlorine atom.

A particularly useful group of compounds according to the invention has the formula (1a):



(1a)

wherein R^1, R^2, R^3, R^4 and R^5 are as defined for formula (1).

One particular class of compounds of formulae (1) and (1a) is that wherein one or both of R^2 and R^3 is a hydrogen atom. Compounds in which R^2 and R^3 is each a hydrogen atom are especially useful.

In compounds of this class R^1 is in particular a group $-(Alk^2)_pNH_2$ (where Alk^2 is as defined above for Alk and p is zero or an integer 1), $-(Alk^2)_pNR^{15}R^{16}$ (where R^{15} and R^{16} are as defined above), $-(Alk^2)_pNHet^2$ (where $-NHet^2$ is as defined above for $NHet^1$), $-(Alk^2)_pOH$, and $-(Alk^2)_pAr$ (where Ar is a nitrogen-containing heteroaromatic group as defined above). Especially useful R^1 substituents include $-Alk^2NH_2$, particularly $-(CH_2)_2NH_2$ and $-C(CH_3)_2NH_2$, $-Alk^2NR^{15}R^{16}$, particularly $-CH_2N(CH_2CH_3)_2$ and $-(CH_2)_2NHC(CH_3)_3$, $-(Alk)^2_pNHet^2$ where $-NHet^2$ is an optionally substituted pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or thiomorpholinyl group, $-Alk^2OH$, particularly $-(CH_2)_2OH$ and $-(Alk^2)_pAr$ where Ar is an optionally substituted imidazolyl or benzimidazolyl group. Optional substituents which may be present on these particular $-NHet^2$ or

Ar groups include thos generally and particularly described above in relation to the groups -NHet^1 and Ar.

In general in compounds of formulae (1) or (1a) R^4 is preferably a group X^1R^{11} in which X^1 is a covalent bond and R^{11} is a phenyl or, especially, a substituted phenyl group containing one, two or three R^{17} substituents as defined herein. Particularly useful R^{17} substituents include $-(Alk^2)_pNH_2$ substituents as just generally and particularly discussed for R^1.

Particularly useful compounds according to the invention include:
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-hydroxyethyl)phenyl] pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[3-(2-hydroxyethyl)phenyl] pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(1-imidazolyl)phenyl] pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)-3-fluorophenyl]-5-chloro-*N*-[4-(2-hydroxyethyl) phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-(imidazol-1-yl)ethyl) phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(2-methylimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(2-isopropylimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-thiomorpholino) ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(tertbutylamino) ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4-methylpiperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4-ethylpiperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(3,5-dimethyl-piperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methyl thyl)phenyl]-5-chloro-N-[4-(2-(4-(pyrid-2-yl) piperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine;

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(pyrrolidin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(piperidin-1-yl)ethyl) phenyl]pyrimidine-2-amine;
(R)-4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(3-dimethyl-aminopyrrolidin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
and the salts, solvates, hydrates and N-oxides thereof.

Compounds according to the invention are potent and selective inhibitors of KDR and/or FGFr4 kinases as demonstrated by differential inhibition of these enzymes when compared to inhibition of other protein kinases such as EGFr kinase, $p56^{lck}$ kinase, ZAP-70 kinase, protein kinase C, Csk kinase and $p59^{fyn}$ kinase. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

The compounds according to the invention are thus of particular use in the prophylaxis and treatment of diseases in which inappropriate KDR kinase action plays a role, for example in disease states associated with angiogenesis. The compounds are then of use for example in the prophylaxis and treatment of cancer, prosiasis, rheumatoid arthritis, Kaposi's Sarcoma, ischemic heart disease, atherosclerosis and occular diseases, such as diabetic retinopathy, involving retinal vessl proliferation and the invention is to be understood to extend to such uses and to the use of a compound of formula (1) in the preparation of a medicament for the prophylaxis and teatment of such diseases.

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formula (1) may be formulated for parenteral administration by injection, including bolus injection or infusion or particle mediated injection. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials or a device containing a compressed gas such as helium for particle mediated administration. The compositions for bolus injection or infusion may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitabl vehicle, e.g. sterile pyrogen-free water, before use. For

particle m diated administration the complex may be coated on particles such as microscopic gold particles.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection. Where desired, the compounds according to the invention may also be conjugated to a polymer, e.g. a naturally occuring polymer such as albumin, to prolong the half life of the compounds when in use. Such conjugates may be formulated and delivered as described above.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

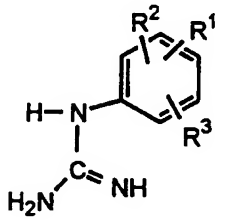
The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds of the invention may be prepar d by a number of process s as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols

R^1, R^2, R^3, R^4 and R^5 when us d in the text or formula depicted are to be understood to represent thos groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1991]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups.

Thus according to a further aspect of the invention, a compound of formula (1) may be prepared by reaction of a guanidine of formula (2):



(2)

or a salt thereof

with an enaminone of formula (3):

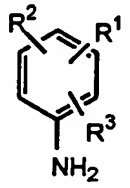
$$R^4COC(R^5)CHN(R^{20})(R^{21}) \qquad (3)$$

where R^{20} and R^{21}, which may be the same or different is each a C_{1-6} Alkyl group.

The reaction may be performed in a solvent, for example a protic solvent such as an alcohol, e.g. ethanol, ethoxyethanol or propan-2-ol, optionally in the presence of a base e.g. an Alkali metal base, such as sodium hydroxide or potassium carbonate, at an elevated temperature, e.g. the reflux temp rature.

Salts of th compounds of formula (2) include acid salts such as inorganic acid salts e.g. hydrochlorides or nitrat s.

Intermediate guanidines of formula (2) may be prepared by reaction of the corresponding amine of formula (4):



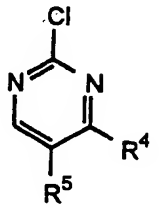
(4)

with cyanamide at an elevated temperature. The reaction may be performed in a solvent such as ethanol at an elevated temperature, e.g. up to the reflux temperature. Where it is desired to obtain a salt of a guanidine of formula (2), the reaction may be performed in the presence of a concentrated acid, e.g. hydrochloric or nitric acid.

The amines of formula (4) are either known compounds or may be obtained by conventional procedures, for example by hydrogenation of the corresponding nitro derivatives using for example hydrogen in the presence of a metal catalyst in a suitable solvent, for example as more particularly described in the interconversion reactions discussed below. The nitrobenzenes for this particular reaction are either known compounds or may be prepared using similar methods to those used for the preparation of the known compounds.

Intermediate enaminones of formula (3) are either known compounds or may be prepared by reaction of an acetyl derivative $R^4COCH_2R^5$ with an acetal $(R^{20})(R^{21})NCH(OR^{22})_2$ (where R^{22} is a C_{1-6}Alkyl group such as a methyl or ethyl group) at an elevated temperature. The starting materials for this reaction are either known compounds or may be prepared by methods analogous to those used for the preparation of the known compounds.

In another process according to the invention, a compound of formula (1) may be prepared by displacement of a chlorine atom in a pyrimidine of formula (5):

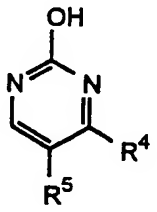


(5)

with an amine of formula (4)

The reaction may be performed at an elevated temperature, for example the reflux temperature, where necessary in the presence of a solvent, for example an alcohol, such as 2-ethoxyethanol or isopopanol, a cyclic ether, e.g. dioxane or a substituted amide such as dimethylformamide, optionally in the presence of a base, for example an organic amine such as pyridine.

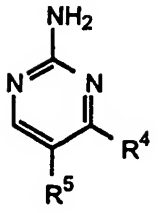
Intermediate pyrimidines of formula (5) may be obtained by reaction of a corresponding pyrimidine of formula (6):



(6)

with phosphorous oxychloride optionally in a solvent such as a substituted amide e.g. dimethylformamide at an elevated temperature, for example the reflux temperature.

Intermediates of formula (6) may be prepared from the corresponding amine of formula (7):



(7)

with sodium nitrite in an aqueous acid,e.g. aqueous sulphuric acid at around ambient temperature.

Amines of formula (7) may be prepared by reaction of an enaminone of formula (3) with a guanidine salt, e.g. guanidine carbonate, as described above for the preparation of compounds of formula (1).

Compounds of formula (1) may also be prepared by interconversion of other compounds of formula (1) and it is to be understood that the invention extends to such interconversion processes. Thus, for example, standard substitution approaches employing for example Alkylation, arylation, heteroarylation, acylation, thioacylation, sulphonylation, formylation or coupling reactions may be used to add new substitutents to and/or extend existing substituents in compounds of formula (1). Alternatively existing substituents in compounds of formula (1) may be modified by for example oxidation, reduction or cleavage reactions to yield other compounds of formula (1).

The following describes in general terms a number of approaches which can be employed to modify existing phenyl and/or other aromatic ot heteroaromatic groups in compounds of formula (1). It will be appreciated that each of these reactions will only be possible where an appropriate functional group exists in a compound of formula (1). Where desired, these reactions may also be performed on intermediates to compounds of formula (1).

Thus, for example Alkylation, arylation or heteroarylation of a compound of formula (1) may be achieved by reaction of the compound with a reagent Alk, L or ArL, where Alk is an Alkyl group and Ar is an aryl or heteroaryl

group as defined above in relation to compounds of formula (1) and L is a leaving atom or group such as a halogen atom, e.g. a chlorine or bromin atom, or a sulphonyloxy group, e.g. an arylsulphonyloxy group such as a *p*-toluenesulphonyloxy group.

The Alkylation or arylation reaction may be carried out in the presence of a base, e.g. an inorganic base such as a carbonate, e.g. caesium or potassium carbonate, an Alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran, at around 0°C to around 40°C.

In a variation of this process the leaving group L may be alternatively part of the compound of formula (1) and the reaction performed with an appropriate nucleophilic reagent at an elevated temperature. Particular nucleophilic reagents include cyclic amines, such as piperazine. Where appropriate the reaction may be performed in a solvent such as an aprotic solvent, e.g. a substituted amide such as dimethylformamide.

In another general example of an interconversion process, a compound of formula (1) may be acylated or thioacylated. The reaction may be performed for example with an acyl halide or anhydride in the presence of a base, such as a tertiary amine e.g. triethylamine in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at for example ambient temperature, or by reaction with a thioester in an inert solvent such as tetrahydrofuran at a low temperature such as around 0°C. The reaction is particularly suitable for use with compounds of formula (1) containing primary or secondary amino groups.

In a further general example of an interconversion process, a compound of formula (1) may be formylated, for example by reaction of the compound with a mixed anhydride $HCOOCOCH_3$ or with a mixture of formic acid and acetic anhydride.

Compounds of formula (1) may be prepared in another general interconversion reaction by sulphonylation, for example by reaction of the

compound with a reagent $AlkS(O)_2L$, or $ArS(O)_2L$ in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature. The reaction may in particular be performed with compounds of formula (1) possessing a primary or secondary amino group.

In further examples of interconversion reactions according to the invention compounds of formula (1) may be prepared from other compounds of formula (1) by modification of existing functional groups in the latter.

Thus in one example, ester groups $-CO_2Alk^1$ in compounds of formula (1) may be converted to the corresponding acid [$-CO_2H$] by acid- or base-catalysed hydrolysis or by catalytic hydrogenation depending on the nature of the group Alk^1. Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an aqueous solvent or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an Alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol. Catalytic hydrogenation may be carried out using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol, e.g. methanol.

In a second example, -OAlk [where Alk represents an Alkyl group such as a methyl group] groups in compounds of formula (1) may be cleaved to the corresponding alcohol -OH by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around -78°C.

In another example, alcohol -OH groups in compounds of formula (1) may be converted to a corresponding -OAlk or -OAr group by coupling with a reagent AlkOH or ArOH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate.

Aminosulphonylamino [-$NHSO_2NH_2$] groups in compounds of formula (1) may be obtained, in another example, by reaction of a corresponding amine [-NH_2] with sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

In another example of an interconversion process secondary amine groups in compounds of formula (1) may be Alkylated using an alcohol, e.g. ethanol and catalytic hydrogenation, employing for example hydrogen in the presence of a metal catalyst such as palladium on a support such as carbon.

In a further example, amine [-NH_2] groups in compounds of formula (1) may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature. In an alternative, amine groups may also be generated by reduction of the corresponding nitrile, for example using a reducing agent such as a borohydride, e.g. sodium borohydride or cerium trichloride.

In another example, a nitro [-NO_2] group may be reduced to an amine [-NH_2], for example by catalytic hydrogenation as just described, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

Where salts of compounds of formula (1) are desired, these may be prepared by conventional means, for example by reaction of a compound of formula (1) with an appropriate acid or base in a suitable solvent or mixture of solvents, e.g. an organic solvent such as an ether, e.g. diethylether, or an alcohol, e.g. ethanol.

The following Examples illustrate the invention. In the Examples all ^{1}Hnmr were run at 300MHz unless specified otherwise. All temperatures are in °C.

The following abbreviations are used:

THF - tetrahydrofuran; DMF - dimethylformamide;
DMSO - dimethylsulphoxide; TFA - trifluoroacetic acid;

EXAMPLE 1

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-hydroxyethyl)phenyl]pyrimidine-2-amine

A mixture of 4-[4-(1-tertbutoxycarbonylamino-1-methylethyl)phenyl]-2,5-dichloropyrimidine (1.53g, 4.0mmol) and 4-aminophenethyl alcohol (1.10g, 8.0mmol) in 2-ethoxyethanol (15ml) was heated to reflux for 18h. The reaction was cooled to room temperature, trifluoroacetic acid (2ml) added and the reaction stirred for 30min. Solvent was removed *in vacuo* and the residue partitioned between CH_2Cl_2 (100ml) and saturated, aqueous Na_2CO_3 (80ml). The aqueous layer was re-extracted with CH_2Cl_2 (2 x 80ml) and the combined CH_2Cl_2 layer washed with aqueous Na_2CO_3 (80ml), brine (80ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, 10-15% methanol in CH_2Cl_2) to give the title compound as a buff solid (1.30g) m.p. 162-163°. δH (d^6DMSO) 9.74 (1H, s), 8.55 (1H, s), 7.76 (2H, d, J 8.5Hz), 7.68 (2H, d, J 8.5Hz), 7.62 (2H, d, J 8.5Hz), 7.12 (2H, d, J 8.5Hz), 4.57 (1H, bs), 3.55 (2H, m), 2.65 (2H, t, J 7.2Hz), 1.41 (6H, s); MS (ESI) 383 (MH^+, ^{35}Cl, 100%).

The 4-[4-(1-tertbutoxycarbonylamino-1-methylethyl)phenyl]-2,5-dichloro pyrimidine used in the above process was prepared as follows:-

Cerium trichloride heptahydrate (22.47g, 60mmol) was dried in a flask under high vacuum (0.08 Torr) heated by an oil bath at 140-160° for 4h. On cooling, nitrogen was introduced slowly into the flask and anhydrous THF (120ml) added to give a suspension of $CeCl_3$ which was stirred for 16h at room temperature. The mixture was cooled to -65°, methyl lithium (37.5ml of a 1.6M solution in diethylether, 60mmol) added dropwise and the mixture stirred for 0.5h. A solution of 4-bromobenzonitrile (3.64g,

20mmol) in THF (10ml) was added and the reaction stirr d at -65° for 3.5h before allowing the mixture to warm to -40°. The reaction was quenched by the addition of 33% ammonium hydroxide (50ml) and then allowed to warm to room temperature. The resulting solids were removed by filtration through a pad of Celite® and were washed with ethyl acetate (3 x 100ml). The combined filtrates were washed with brine (20ml), the organic phase dried ($MgSO_4$) and concentrated *in vacuo* to give 1-(4-bromophenyl)-1-methylethylamine as a yellow oil (4.01g). This product was heated at reflux in toluene (40ml) with di-tert-butyl dicarbonate (4.50g, 20.6mmol) for 1h. Solvent was removed *in vacuo* and the crude product recrystallised from hexane at -20° to give tertbutyl N-{1-(4-bromophenyl)-1-methylethyl}carbamate as colourless crystals (3.47g) m.p. 92-93° δH ($CDCl_3$) 7.43 (2H, dt, J 8.7, 2.7Hz), 7.26 (2H, dt, J 8.8, 2.6Hz), 4.91 (1H, bs), 1.59 (6H, s), 1.36 (9H, bs).

A mixture of tert-butyl N-{1-(4-bromophenyl)-1-methylethyl}carbamate (1.57g, 5.0mmol), bis(pinacolato)diboron (1.40g, 5.5mmol), [1,1'-bis (diphenylphosphino)ferrocene]dichloropalladium(II) (123mg, 0.015mmol) and potassium acetate (1.47g, 15.0mmol) was dissolved in dry DMF (20ml) under nitrogen and heated to 80° for 5h. The reaction was then concentrated under reduced pressure, the resulting residue taken up in dichloromethane (80ml) and washed with water (1 x 80ml), then brine (1 x 80ml), dried ($MgSO_4$) and again concentrated. The residue was subjected to column chromatography (silica gel; 15% ethyl acetate-hexane) to give tert-butyl N-{1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methylethyl}carbamate (1.55g) as a white solid m.p. 140°. δH ($CDCl_3$) 7.77 (2H, d, J 8.3Hz), 7.40 (2H, d, J 8.4Hz), 1.63 (6H, s) and 1.34 (21H, s).

2M aqueous Na_2CO_3 (4.7ml, 9.4mmol) was added to a solution of 2,4,5-trichloropyrimidine [Chesterfield, J.; McOmie, J. F. W.; Sayer, E. R.; J. Chem. Soc. (1955) 3478-3481] (1.18g, 6.44mmol), tert-butyl N-{1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]1-methylethyl} carbamate (1.55g, 4.29mmol) and tetrakis(triphenylphosphine)palladium (O) (150mg, 0.13mmol) in ethyleneglycol dimethylether (20ml) under N_2 and the mixture heated to reflux for 6h. The reaction was diluted with H_2O (30ml) and xtracted with ethyl acetat (3 x 50ml), the combined ethyl acetate extracts wer washed with brine (30ml), dri d ($MgSO_4$) and

concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 15% ethyl acetate in hexane) to giv 4-[4-(1-tert-butoxycarbonylamino-1-methylethyl)phenyl]-2,5-dichloropyrimidine as a white solid (1.34g). δH (d^6DMSO) 8.62 (1H, s), 7.90 (2H, d, J 8.6Hz), 7.54 (2H, dt, J 8.7, 2.1Hz), 5.02 (1H, bs), 1.65 (6H, s) and 1.37 (9H, s).

EXAMPLE 2

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[3-(2-hydroxyethyl) phenyl]pyrimidine-2-amine

The title compound was prepared from 4-[4-(1-tert-butoxycarbonylamino-1-methylethyl)phenyl]-2,5-dichloropyrimidine (1.50g, 6.55mmol) and 2-(3-aminophenyl)ethanol (942mg, 6.87mmol) following the method of Example 1. The crude product was purified by chromatography (Silica, 10% methanol in CH_2Cl_2) to give the title compound as a brown solid (600mg) m.p. 184-185°. δH (d^6DMSO) 9.77 (1H, s), 8.57 (1H, s), 7.79 (2H, d, J 8.4Hz), 7.68 (2H, d, J 8.4Hz), 7.61-7.58 (2H, m), 7.17 (1H, t, J 7.7Hz), 6.82 (1H, d, J 7.4Hz), 4.62 (1H, bs), 3.60 (2H, t, J 7.0Hz), 2.68 (2H, t, J 7.1Hz), 2.07 (2H, bs), 1.41 (6H, s); MS (ESI) 383 (MH^+, ^{35}Cl).

EXAMPLE 3

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(1-imidazolyl) phenyl]pyrimidine-2-amine

Sodium hydride (330mg, 8.25mmol) was added to a solution of 4-[4-(1-tert-butoxycarbonylamino-1-methylethyl)phenyl]-2,5-dichloropyrimidine (1.0g, 2.62mmol) and 1-(4-aminophenyl)-1H-imidazole (438mg, 2.75mmol) in dry THF (40ml) under N_2 and the mixture heated to reflux for 3h. The reaction was quenched with H_2O (5ml), diluted with brine (50ml) and extracted with ethyl acetate (2 x 150ml). The ethyl acetate extracts were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by column chromatography (silica; 2% ethyl acetate in CH_2Cl_2) to give 4-[4-(1-tert-butoxy carbonylamino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(1-imidazolyl)-phenyl] pyrimidine-2-amine as a yellow solid (310mg) m.p. 218-220°. This intermediate was stirrd at room temperature in trifluoroacetic acid (4ml) for 3h before concentrating the reaction *in vacuo*. Th residue was diluted with 2M NaOH (aq) (50ml) and extracted with CH_2Cl_2-ethanol (20:1) (3 x 50ml), the extracts dried ($MgSO_4$) and concentrated *in vacuo*. Trituration

of the resultant solid with diethylether-ethyl ac tate (4:1) gave the title compound as a pale yellow solid (175mg) m.p. 199-201°. δH (d^6DMSO) 10.05 (1H, bs), 8.62 (1H, s),8.15 (1H, s), 7.88 (2H, d, J 7.9Hz), 7.78 (2H, d, J 8.5Hz), 7.69 (2H, d, J 8.5Hz), 7.65 (1H, s), 7.55 (2H, d, J 8.8Hz), 1.42 (6H, s). MS (ESI) 405 (MH^+, 100%).

1-(4-Aminophenyl)-1H-imidazole used in the above process was prepared by suspending 1-(4-nitrophenyl)-1*H*-imidazole (10.0g, 52.86mmol) and 10% Pd on carbon (1g) in ethanol (125ml). The mixture was degassed with N_2 and subjected to an atmosphere of hydrogen (balloon) for 24h at room temperature with magnetic stirring. The reaction was filtered through Celite®, washing the filter cake with ethanol (125ml) and the filtrates concentrated *in vacuo* to give 1-(4-aminophenyl)-1H-imidazole as an off white solid (8.02g) m.p. 156-157°.

EXAMPLE 4

4-[4-(1-Amino-1-methylethyl)-3-fluorophenyl]-5-chloro-*N*-[4-(2-hydroxyethyl)phenyl]pyrimidine-2-amine

The title compound was prepared from 4-[4-(1-tert-butoxycarbonylamino-1-methylethyl)-3-fluorophenyl]-2,5-dichloropyrimidine (1.60g, 4.0mmol) and 4-aminophenethyl alcohol (826mg, 6.0mmol) following the method of Example 1.

The crude product was purified by column chromatography (silica; 5-10% MeOH in CH_2Cl_2) to give the title compound as a light brown solid (920mg) m.p. 172-176°. δH ($CDCl_3$) 8.43 (1H, s), 7.67 (1H, dd, J 8.2, 1.8Hz), 7.62-7.55 (4H, m), 7.22 (2H, d, J 8.5Hz), 7.19 (1H, bs), 3.86 (2H, t, J 6.5Hz), 2.86 (2H, t, J 6.5Hz), 1.68 (2H, bs), 1.60 (6H, s). MS (ESI) 401 (MH^+).

The intermediate 4-[4-(1-tertbutoxycarbonylamino-1-methylethyl)-3-fluorophenyl]-2,5-dichloropyrimidine in the above process was prepared using the same methods described for its analogue in Example 1. Thus starting from 4-bromo-2-fluorobenzonitrile the following intermediates were prepared:

tert-Butyl *N*-{1-(4-bromo-2-fluorophenyl)-1-methylethyl}carbamate as an off white solid δH ($CDCl_3$) 7.25-7.16 (3H, m), 4.98 (1H, bs), 1.66 (6H, s), 1.36 (9H, bs).

tert-Butyl *N*-{1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxanborolan-2-yl)-2-

fluorophenyl]-1-methylethyl}carbamate as a white solid δH ($CDCl_3$) 7.51 (1H, dd, J 7.7, 1.1Hz), 7.42 (1H, dd, J 13.0, 1.1Hz), 7.34 (1H, t, J 8.0Hz), 5.01 (1H, bs), 1.68 (6H, s), 1.33 (21H, bs).

4-[4-(1-tertButoxycarbonylamino-1-methylethyl)-3-fluorophenyl]-2,5-dichloropyrimidine m.p. 148-149°. δH ($CDCl_3$) 8.65 (1H, s). 7.72 (1H, dd, J 8.3, 1.9Hz), 7.64 (1H, dd, J 13.1, 1.8Hz), 7.50 (1H, t, J 8.3Hz), 5.04 (1H, bs), 1.72 (6H, s), 1.37 (9H, s) MS (ESI) 422 (MNa^+).

EXAMPLE 5

4-[4-(1-Allyloxycarbonylamino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-(imidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine

p-Toluenesulphonyl chloride (867mg, 4.55mmol) was added to a solution of 4-[4-(1-allyloxycarbonylamino-1-methylethyl)phenyl-5-chloro-*N*-[4-(2-hydroxyethyl)phenyl]pyrimidine-2-amine (1.16g, 3.03mmol), pyridine (2.45ml, 30.3mmol) and 4-dimethylaminopyridine (50mg) in CH_2Cl_2 (25ml). The reaction was stirred at room temperature under N_2 for 18h before diluting with CH_2Cl_2 (50ml). The dichloromethane solution was washed with 2M hydrochloric acid (2 x 80ml), brine (80ml), dried ($MgSO_4$) and concentrated *in vacuo* to give a thick oil. Column chromatography (silica; 35% ethyl acetate in hexane) gave 4-[4-(1-allyloxycarbonylamino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-ptoluenesulphonyloxyethyl)phenyl] pyrimidine-2-amine as a pale yellow solid (1.40g). δH ($CDCl_3$) 8.42 (1H, s), 7.89 (2H, d, J 8.5Hz), 7.70 (2H, dt, J 8.4, 1.8Hz), 7.56-7.51 (5H, m), 7.28 (2H, d, J 8.6Hz), 7.09 (2H, d, J 8.5Hz), 5.90 (1H, bs), 5.32 (1H, bs), 5.21 (2H,s), 4.51 (2H, d, J 5.5Hz), 4.20 (2H, t, J 7.1Hz), 2.93 (2H, t, J 7.1Hz), 2.41 (3H,s), 1.71 (6H, s).

To the tosylate prepared above (1.0g, 1.61mmol) in dry DMF (20ml) under N_2 was added imidazole (1.03g, 15.2mmol) and the mixture heated to 80° for 18h. Solvent was removed *in vacuo* and the residue dissolved in CH_2Cl_2 (80ml), washed with aqueous Na_2CO_3 (3 x 20ml), brine (20ml), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (silica; 5% methanol in CH_2Cl_2) gave 4-[4-(1-allyloxycarbonylamino-1-methylethyl) phenyl]-5-chloro-*N*-[4-(2-imidazol-1-ylethyl)phenyl]pyrimidine-2-amine as a yellow solid (670mg) m.p. 72-78°. δH ($CDCl_3$) 8.41 (1H, s) 7.88 (2H, d, J 8.6Hz), 7.61-7.52 (4H, m), 7.35 (1H, bs), 7.21 (2H, d, J

8.5Hz), 5.89 (1H, bs), 5.39-5.13 (3H, m), 4.50 (2H, d, J 5.6Hz), 3.86 (2H, t, J 6.5Hz), 2.85 (2H, t, J 6.5Hz), 1.71 (6H, s). MS (ESI) 517 (MH^+, 100%).

The intermediate 4-[4-(1-allyloxycarbonylamino-1-methylethyl)phenyl-5-chloro-*N*-[4-(2-hydroxy-ethyl)phenyl]pyrimidine-2-amine used in the above process was prepared as follows:

To a solution of the compound of Example 1 (1.20g, 3.1mmol) in CH_2Cl_2 (40ml) was added saturated, aqueous Na_2CO_3 (20ml) and allylchloroformate (410mg, 3.4mmol) and the reaction stirred at room temperature for 2h. The CH_2Cl_2 layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (silica; 5% methanol in CH_2Cl_2) to give the desired intermediate as a yellow solid (1.23g). δH ($CDCl_3$) 8.41 (1H, s), 7.88 (2H, d, J 8.6Hz), 7.61-7.51 (4H, m), 7.35 (1H, bs), 7.21 (2H, d, J 8.5Hz), 6.91 (1H, bs) 5.40-5.18 (3H, m), 4.50 (2H, d, J 5.6Hz), 3.86 (2H, t, J 6.5Hz), 2.85 (2H, t, J 6.5Hz), 1.71 (6H, s). MS (ESI) 467 (MH^+, 100%).

EXAMPLE 6

4-[4-(1-Allyloxycarbonylamino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-morpholinoethyl)phenyl]pyrimidine-2-amine

A mixture of the tosylate prepared in Example 5 (400mg, 0.64mmol) and morpholine (0.28ml, 3.22mmol) was heated to reflux in dry THF (10ml) under N_2 for 18h. The reaction was diluted with ethyl acetate (40ml), washed with saturated, aqueous Na_2CO_3 (2 x 20ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (4% methanol in CH_2Cl_2) to give the title compound as a yellow solid (310mg) m.p. 65-69° δH ($CDCl_3$) 8.41 (1H, s) 7.88 (2H, d, J 8.5Hz), 7.57-7.52 (4H, m), 7.19 (2H, d, J 8.4Hz), 7.18 (1H, obscured by over-lapping signal), 5.88 (1H, bs), 5.36-5.19 (3H, m), 4.50 (2H, d, J 5.6Hz), 3.85 (4H, bs), 3.06-2.43 (8H, m), 1.71 (6H, s).

EXAMPLE 7

4-[4-(1-Allyloxycarbonylamino-1-methylethyl)-3-fluorophenyl]-5-chloro-*N*-[4-(2-(imidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine

The title compound was prepared from 4-[4-(1-allyloxycarbonylamino-1-methylethyl)-3-fluoroph nyl]-5-chloro-*N*-[4-(2-p-toluenesulphonyloxyethyl)-phenyl]pyrimidine-2-amine (504mg, 0.79mmol) and imidazole (337mg,

4.95 mmol) following th method described for Exampl 5. Th crude product was purifi d by column chromatography (silica; 5% methanol in CH_2Cl_2) to give the title compound as a yellow solid (330mg) m.p. 88° forms gum. δH ($CDCl_3$) 8.43 (1H, s), 7.69 (1H, dd, J 8.2, 1.8Hz), 7.61 (1H, dd, J 13.3, 1.8Hz), 7.54 (2H, d, with fine splitting, J 8.6Hz), 7.50 (1H, t, J 8.5Hz), 7.34 (1H, s), 7.18 (1H, s), 7.04 (3H, m), 5.89 (1H, bs), 5.30-5.12 (3H, m), 4.50 (2H, dt, J 5.6, 1.4Hz), 4.16 (2H, t, J 7.1Hz), 3.03 (2H, t, J 7.0Hz), 1.78 (6H, s); MS (ESI) 535 (MH^+, 100%).

The intermediate tosylate used in the above process was prepared using the same methods described for its analogue in Example 5: thus starting from the compound of Example 4 the following intermediates were prepared:

4-[4-(1-Allyloxycarbonylamino-1-methylethyl)-3-fluorophenyl-5-chloro-*N*-[4-(2-hydroxyethyl)phenyl]pyrimidine-2-amine as a yellow solid. δH ($CDCl_3$) 8.42 (1H, s), 7.69 (1H, d, J 8.2Hz), 7.61 (1H, d, J 13.4Hz), 7.56 (2H, d, J 8.4Hz), 7.49 (1H, t, J 8.4Hz), 7.22 (2H, d, J 8.5Hz), 7.21 (1H, bs), 5.88 (1H, bs), 5.30 (1H, s), 5.29-5.16 (2H, m), 4.49 (2H, m), 3.86 (2H, t, J 6.3Hz), 2.86 (2H, t, J 6.3Hz), 1.78 (6H, s); MS (ESI) 485 (MH^+, 100%).

4-[4-(1-Allyloxycarbonylamino-1-methylethyl)-3-fluorophenyl]-5-chloro-*N*-[4-(2-ptoluenesulphonyloxyethyl)phenyl]pyrimidine-2-amine as a yellow solid. δH ($CDCl_3$) 8.43 (1H, s), 7.70 (4H, m), 7.62 (1H, dd, J 13.3, 1.8Hz), 7.54-7.48 (3H, m), 7.29 (2H, d, J 8.0Hz), 7.10 (2H, d, J 8.5Hz), 5.88 (1H, bs), 5.33-5.12 (3H, m), 4.51 (2H, m), 4.20 (2H, t, J 7.1Hz), 2.94 (2H, t, J 7.0Hz), 2.42 (3H, s), 1.78 (6H, s).

EXAMPLE 8

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-(imidazol-1-yl) ethyl)phenyl]pyrimidine-2-amine

Tetrakis(triphenylphosphine)palladium(0) (147mg, 0.13mmol) was added to a solution of the compound of Example 5 (655mg, 1.27mmol) and 5,5-dimethyl-1,3-cyclohexanedione (1.42g, 10.15mmol) in anhydrous THF (20ml) under N_2. The reaction was stirred for 30min at room temperature and was then diluted with ethyl acetate (50ml), washed with 2M aqueous NaOH (3 x 20ml), brine (20ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (Silica; 10% methanol in CH_2Cl_2) to give the title compound as a yellow solid (380mg).

δH ($CDCl_3$) m 8.41 (1H, s), 7.86 (2H, d, J 8.5Hz), 7.64 (2H, d, J 8.5Hz), 7.55 (2H, d, J 8.5Hz), 7.36 (1H, bs), 7.34 (1H, bs), 6.99 (3H, m), 6.83 (1H, bs), 4.14 (2H, m), 3.00 (2H, t, J 7.0Hz), 2.72 (2H, bs), 1.57 (6H, s). MS (ESI) 433 (MH^+, 100%).

The following examples 9 and 10 were prepared by the method described for Example 8.

EXAMPLE 9

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-morpholinoethyl)phenyl]pyrimidine-2-amine

From the compound of Example 6 (310mg, 0.58mmol), tetrakis-(triphenylphosphine)palladium(O) (60mg, 0.06mmol) and 5,5-dimethyl-1,3-cyclohexadione (650mg, 4.64mmol) to give the title compound as a pale yellow solid (240mg) m.p. 166-173° δH ($CDCl_3$) 8.40 (1H, s), 7.87 (2H, d, J 8.4Hz), 7.65 (2H, d, J 8.3Hz), 7.53 (2H, d, J 8.3Hz), 7.24 (1H, bs), 7.17 (2H, d, J 8.4Hz), 3.75 (4H, m), 2.78 (2H, m), 2.58 (8H, m), 1.58 (6H, s). MS (ESI) 452 (MH^+).

EXAMPLE 10

4-[4-(1-Amino-1-methylethyl)-3-fluorophenyl]-5-chloro-*N*-[4-(2-(imidazol-1-yl)ethyl)phenyl]pyrimidine 2-amine

From the compound of Example 7 (330mg, 0.62mmol) tetrakis-(triphenylphosphine)palladium(O) (71mg, 0.062mmol) and 5,5-dimethyl-1,3-cyclohexadione (692mg, 4.94mmol) to give after chromatography (Silica; 8% methanol in CH_2Cl_2) the title compound as a yellow solid (200mg) m.p. 112-120° δH (d^6 DMSO) 9.85 (1H, s), 8.60 (1H, s), 7.77 (1H, t, J 8.4Hz), 7.62 (2H, d, J 8.5Hz), 7.57 (1H, s, with fine splitting), 7.52 (1H, d, J 1.7Hz), 7.48 (1H, s), 7.12 (1H, s), 7.08 (2H, d, J 8.5Hz), 6.83 (1H, s), 4.16 (2H, t, J 7.4Hz), 2.95 (2H, t, J 7.5Hz), 1.46 (6H, s), MS (ESI) 451 (MH^+).

EXAMPLE 11

Resin bound 4-[4-(1-tertbutoxycarbonylamino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-hydroxyethyl)phenyl]pyrimidine-2-amine (1)

A slurry of polystyrene sulphonyl chlorid resin (Argonaut Technologies, 520mg, 2.4mmol/g, 1.24mmol equivalent) in anhydrous dichloromethane (12ml) was treated with 4-[4-(1-tertbutoxycarbonylamino-1-methylethyl) phenyl]-5-chloro-N-[4-(2-hydroxyethyl)phenyl]pyrimidine-2-amine (2.40g, 4.97mmol), N,N-diethylisopropylamine (0.64g, 4.97mmol) and anhydrous pyridine (4mL) and the resulting mixture agitated at room temperature for 18h. The resin was filtered and washed sequentially with dichloromethane, methanol, N,N-dimethylformamide and dichloromethane then air dried to give the sulphonate derivatised resin (1).

EXAMPLE 12

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(2-methylimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine

A mixture of derivatised resin (1) (55mg), N,N-diethylisopropylamine (38mg, 0.30mmol), and 2-methylimidazole (8mg, 0.10mmol) in anhydrous acetonitrile (2ml) was heated at 70° for 18h, with agitation. The mixture was allowed to cool to room temperature then diluted with anhydrous tetrahydrofuran (2ml) and treated with polystyrene methylisocyanate (Argonaut Technologies, 120mg, 1.65mmol/g, 0.2mmol equivalent) and macroporous triethylammonium methylpolystyrene carbonate (Argonaut Technologies, 38mg, 2.64mmol/g, 0.1mmol equivalent). The resulting mixture was agitated at room temperature for 6h, then filtered and washed once with dichloromethane. The combined filtrate and washings were evaporated to dryness under a stream of nitrogen, then resuspended in dichloromethane (1mL) and treated with trifluoroacetic acid (1mL) for 1h at room temperature. The mixture was evaporated to give the title compound (19.4mg).

HPLC-MS Retention time 1.93min; MH+ 447

HPLC-MS

HPLC-MS was performed on a Hewlett Packard 1100/MSD ES Single Quadropole system with diode array detector using a Luna C18(2) 50 x 2.0mm (3μm) column, running a gradient of 95% [0.1% aqueous formic acid], 5% [0.1% formic acid in acetonitrile] to 10% [0.1% aqueous formic acid], 90% [0.1% formic acid in acetonitril] over 2min, then maintaining the mobile phase at that ratio for a further 1min. Flow rate 0.8ml/min. MS

was acquired by API lectrospray in positiv ion mode, at 70V, scanning from 150 to 750amu.

The following compounds of examples 13 to 25 were prepared in a similar manner to the compound of example 12, each using the starting material shown in place of 2-methylimidazole:

EXAMPLE 13

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(2-ethylimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine

2-Ethylimidazole gave the title compound (16.1mg)

HPLC-MS Retention time 1.96min; MH+ 461

EXAMPLE 14

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(2-isopropylimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine

2-Isopropylimidazole gave the title compound (12.8mg)

HPLC-MS Retention time 1.98min; MH+ 475

EXAMPLE 15

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4,5-dichloroimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine

4,5-Dichloroimidazole gave the title compound (20.4mg)

HPLC-MS Retention time 2.27min; MH+ 501

EXAMPLE 16

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(benzimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine

Benzimidazole gave the title compound (16.4mg)

HPLC-MS Retention time 2.04min; MH+ 483

EXAMPLE 17

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(thiomorpholino)ethyl)phenyl]pyrimidine-2-amine

Thiomorpholine gave the title compound (22.0mg)

HPLC-MS Retention time 1.93min; MH+ 468

EXAMPLE 18

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(tertbutylamino)ethyl)phenyl]pyrimidine-2-amine

tertButylamine gave the title compound (20.4mg)
HPLC-MS Retention time 1.94min; MH+ 438

EXAMPLE 19

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4-methylpiperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine

1-Methylpiperazine gave the title compound (17.4mg)
HPLC-MS Retention time 1.84min; MH+ 465

EXAMPLE 20

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4-ethylpiperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine

1-Ethylpiperazine gave the title compound (22.1mg)
HPLC-MS Retention time 1.85min; MH+ 479

EXAMPLE 21

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(3,5-dimethylpiperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine

2,6-Dimethylpiperazine gave the title compound (3.1mg)
HPLC-MS Retention time 1.93min; MH+ 479

EXAMPLE 22

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4-(pyrid-2-yl)piperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine

4-(Pyrid-2-yl)piperazine gave the title compound (15.3mg)
HPLC-MS Retention time 1.92min; MH+ 528

EXAMPLE 23

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(pyrrolidin-1-yl)ethyl)phenyl]pyrimidine-2-amine

Pyrrolidine gave the title compound (5.6mg)
HPLC-MS Retention time 1.93min; MH+ 436

EXAMPLE 24

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(piperidin-1-yl)ethyl)phenyl]pyrimidine-2-amine

Piperidine gave the title compound (19.1mg)
HPLC-MS Retention time 1.94min; MH+ 450

EXAMPLE 25

(R)-4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(3-dimethylaminopyrrolidin-1-yl)ethyl)phenyl]pyrimidine-2-amine

(R)-3-Dimethylaminopyrrolidine gave the title compound (23.1mg)
HPLC-MS Retention time 1.75min; MH+ 479

EXAMPLE 26

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-morphoinoethyl)phenyl]pyrimidine-2-amine maleic acid salt

To a hot solution of the compound of Example 9 (50mg, 0.11mmol) in ethanol (2ml) was added a solution of maleic acid (13mg, 0.11mol) in ethanol (1ml) and the mxiture stirred at room temperature for 1h. The solution was partially concentrated *in vacuo* and diethyl ether added to give the desired product as a white precipitate. The precipitate was collected by filtration and washed with diethyl ether to give the title compound as a white solid (49mg). m.p. 179-182°. δH (d^6 DMSO) 9.85 (1H, s), 8.64 (1H, s), 8.32 (1H, bs), 7.94 (2H, d, J 8.5Hz), 7.71 (2H, d, J 8.5Hz), 7.64 (2H, d, J 8.5Hz), 7.15 (2H, d, J 8.5Hz), 6.02 (2H, s), 3.61 (4H, bs), 3.31 (3H, bs), 2.69-2.50 (8H, m), 1.69 (6H, s).

BIOLOGICAL ACTIVITY

The following assays were used to demonstrate the activity and selectivity of compounds according to the invention:

The activity of the comounds against KDR kinase and FGFR2 kinase can be determined in the following two assays:

KDR Kinase and FGFr2 Kinase

The activities of recombinant KDR kinase and FGFr2 kinase were determined by measuring their ability to transfer the γ-phosphate from [^{33}P]ATP to polyglutamic acid - tyrosine (pEY).

The assay methodology employed for both kinases is identical except that in the assay of KDR kinase the diluent used throughout was 20mM HEPES pH 7.25 containing 2mM $MnCl_2$, 2mM $MnCl_2$, 5mM DTT and 0.05% Brij 35, whereas in the FGFr2 assay 10mM $MnCl_2$ is used instead of 2mM $MnCl_2$ and 2mM $MnCl_2$.

The assay was conducted in a total volume of 202µl containing 1-10ng kinase, 5µg/ml pEY (4:1) (Sigma, UK), 1µM ATP (containing ~50,000cpm [^{33}P]ATP (Amersham International, UK) (Sigma, UK) and test inhibitors at the appropriate concentration. The test inhibitors were dissolved in DMSO and added such that the final concentration of DMSO in the assay did not exceed 2% (v/v). The assay was initiated by addition of kinase and terminated after 10 minutes incubation at room temperature by addition of 50µl of 20mM HEPES pH 7.25 containing 0.125M EDTA and 10mM ATP. A 200µl aliquot was applied to the well of a Millipore (UK) MAFC filter plate containing 100µl of 30% (w/v) trichloroacetic acid (TCA). The plate was then placed on a suitable manifold and connected to a vacuum. After complete elimination of the liquid each well was washed under vacuum using five volumes (100µl per wash) of 10% (w/v) TCA and finally two volumes (100µl per wash) of ethanol. The bottom of the filter plate was then sealed and 100µl per well of Ultima Gold (Beckham, UK) scintillant was added to each well. The readioactivity was measured using an appropiate scintillation counter such as a Wallac Trilux or Packard TopCount. The IC_{50} value for each inhibitor was obtained from log dose inhibition curves fitted to the four-parameters logistic equation.

In this assay the most active compounds accoding to the invention have IC_{50} values of around 1µM and below.

The selectivity of compounds according to the invention can be determin d in th following assays:

p56^{lck} kinase assay

The tyrosine kinase activity of p56^{lck} was determined using a RR-src peptide (RRLIEDNEYTARG) and [γ-^{33}P]ATP as substrates. Quantitation of the ^{33}P-phosphorylated peptide formed by the action of p56^{lck} was achieved using an adaption of the method of Geissler *et al* (J. Biol. Chem. (1990) 265, 22255-22261).

All assays were performed in 20mM HEPES pH 7.5 containing 10mM $MgCl_2$, 10mM $MnCl_2$, 0.05% Brij, 1μM ATP (0.5μCi[γ-^{33}P]ATP) and 0.8mg/ml RR-src. Inhibitors in dimethylsulphoxide (DMSO) were added such that the final concentration of DMSO did not exceed 1%, and enzyme such that the consumption of ATP was less than 10%. After incubation at 30°C for 15min, the reaction was terminated by the addition of one-third volume of stop reagent (0.25mM EDTA and 33mM ATP in dH_2O). A 15μl aliquot was removed, spotted onto a P-30 filtermat (Wallac, Milton Keynes, UK), and washed sequentially with 1% acetic acid and de-ionised water to remove ATP. The bound ^{33}P-RR-src was quantitated by scintillation counting of the filtermat in a Betaplate scintillation counter (Wallac, Milton Keynes, UK) after addition of Meltilex scintillant (Wallac, Milton Keynes, UK).

The dpm obtained, being directly proportional to the amount of ^{33}P-RR-src produced by p56^{lck}, were used to determine the IC_{50} for each compound. The IC_{50} was defined as the concentration of compound required to reduce the production of ^{33}P-RR-src by 50%.

In this test, compounds according to the invention have IC_{50} values of 10μM and above.

Zap-70 kinase assay

The tyrosine kinase activity of Zap-70 was determined using a capture assay based on that employed above for p56^{lck}. The RR-src peptide was replaced with polyGlu-Tyr (Sigma; Poole, UK) at a final concentration of 17 μg/ml. After addition of the stopped reaction to the filtermat, trichloroacetic acid 10% (w/v) was employed as th wash reagent instead of acetic acid

and a final wash in absolut ethanol was also perform d before scintillation counting. IC_{50} values were d termined as described ab ve in the $p56^{lck}$ assay.

In this test the compounds of the invention have IC_{50} values of around 10μM and above.

EGFr kinase assay

The tyrosine kinase activity of the EGF receptor (EGFr) was determined using a similar methodology to the $p56^{lck}$ kinase assay, except that the RR-src peptide was replaced by a peptide substrate for EGFr obtained from Amersham International plc (Little Chalfont, UK) and used at the manufacturer's recommended concentration. IC_{50} values were determined as described previously in the $p56^{lck}$ assay.

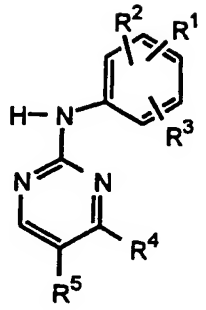
Protein kinase C assay

Inhibitor activity against protein kinase C (PKC) was determined using PKC obtained from Sigma Chemical Company (Poole, UK) and a commercially available assay system (Amersham International plc, Amersham, UK). Briefly, PKC catalyses the transfer of the γ-phosphate (^{32}p) of ATP to the threonine group on a peptide specific for PKC. Phosphorylated peptide is bound to phosphocellulose paper and subsequently quantified by scintillation counting. The inhibitor potency is expressed as either (i) the concentration required to inhibit 50% of the enzyme activity (IC_{50}) or (ii) the percentage inhibition achieved by 10μM inhibitor.

In this test the compounds of the invention have IC_{50} values of around 10μM and above.

CLAIMS

1. A compound of formula (1):



(1)

wherein R^1 is a $-XR^6$ group [where X is a covalent bond, -O-, -S-, -C(O)-, -C(S)-, -C(O)O-, -S(O)-, $-S(O_2)-$, $-CH_2-$, -or $N(R^7)-$ [where R^7 is a hydrogen atom or a straight or branched alkyl group] and R^6 is a hydrogen or halogen atom or an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group, or a $-NO_2$, -CN, $-SO_2N(R^8)(R^9)$ [where R^8 and R^9, which may be the same or different is a hydrogen atom or an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group], $-CON(R^8)(R^9)$, $-CSN(R^8)(R^9)$, $-NH_2$ or substituted amino group;

R^2 and R^3 which may be the same or different is each a hydrogen or halogen atom or a group selected from an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, -OH, $-OR^{10}$ [where R^{10} is an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group] -SH, $-NO_2$, -CN, $-SR^{10}$, $-COR^{10}$, $S(O)R^{10}$, $-SO_2R^8$, $-SO_2N(R^8)(R^9)$, $-CO_2R^8$, $-CON(R^8)(R^9)$, $-CSN(R^8)(R^9)$, $-NH_2$ or substituted amino group;

R^4 is a X^1R^{11} group where X^1 is a covalent bond or a $-C(R^{12})(R^{13})-$ [where each of R^{12} and R^{13} is a hydrogen or halogen atom or a hydroxyl, alkyl or haloalkyl group] or -C(O)- group and R^{11} is an optionally substituted phenyl, thienyl, thiazolyl or indolyl group;

R^5 is a halogen atom or an alkynyl group;

and the salts, solvates, hydrates and N-oxides th reof.

2. A compound according to Claim 1 wherein R^5 is a bromine or chlorine atom.

3. A compound according to Claim 1 or Claim 2 wherein R^4 is a X^1R^{11} group in which X^1 is a covalent bond.

4. A compound according to any one of Claim 1 to Claim 3 wherein R^4 is a X^1R^{11} group and R^{11} is a phenyl or substituted phenyl group containing one, two, or three R^{17} substituents in which each R^{17} sustituent is an atom or group R^{18} or $-Alk(R^{18})_m$, where R^{18} is a halogen atom, or an amino ($-NH_2$), $-NHR^{19}$ [where R^{19} is an $-Alk(R^{18})_m$, heterocycloaliphatic, -Alk-heterocycloaliphatic, aryl or heteroaryl group], $-N(R^{19})_2$ [where each R^{19} group is the same or different], nitro, cyano, hydroxyl (-OH), $-OR^{19}$, formyl, carboxyl ($-CO_2H$), esterified carboxyl, thiol (-SH), $-SR^{19}$, $-COR^{19}$, $-CSR^{19}$, $-SO_3H$, $-SO_2R^{19}$, $-SO_2NH_2$, $-SO_2NHR^{19}$, $SO_2N[R^{19}]_2$, $-CONH_2$, $-CSNH_2$, $-CONHR^{19}$, $-CSNHR^{19}$, $-CON[R^{19}]_2$, $-CSN[R^{19}]_2$, $-N(R^{14})SO_2H$ [where R^{14} is a hydrogen atom or a C_{1-6}alkyl group], $-N(R^{14})SO_2R^{19}$, $-N[SO_2R^{19}]_2$, $-N(R^{14})SO_2NH_2$, $-N(R^{14})SO_2NHR^{19}$, $-N(R^{14})SO_2N[R^{19}]_2$, $-N(R^{14})COR^{19}$, $-N(R^{14})CONH_2$, $-N(R^{14})CONHR^{19}$, $-N(R^{14})CON[R^{19}]_2$, $-N(R^{14})CSR^{19}$, $-N(R^{14})CSNH_2$, $-N(R^{14})CSNHR^{19}$, $-N(R^{14})CSN[R^{19}]_2$, $-N(R^{14})C(O)OR^{19}$, or an optionally substituted cycloaliphatic, heterocycloaliphatic, aryl or heteroaryl group; Alk is a straight or branched C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms or S(O)-, $-S(O)_2-$ or $-N(R^{14})-$ groups; and m is zero or an integer 1, 2 or 3.

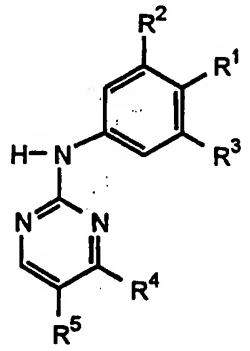
5. A compound according to any one of Claim 1 to Claim 4 wherein one or both of R^2 and R^3 is a hydrogen atom.

6. A compound according to Claim 5 wherein R^2 and R^3 is each a hydrogen atom.

7. A compound according to any on of Claim 1 to Claim 6 wherein R^1 is a group $-(Alk^2)_pNH_2$ (where Alk^2 is a straight or branched C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene chain, optionally substituted by one, two or three -O- or-S- atoms or -S(O)-, $-S(O)_2-$ or $-N(R^{14})-$ group [where R^{14} is a hydrogen atom or a C_{1-6}alkyl group] and p is zero or an integer 1), $-(Alk^2)_pNR^{15}R^{16}$ [where R^{15} is an optionally substituted C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl group optionally interrupted by an -O- or -S- atom or a -C(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^{14})-$, $-CON(R^{14})-$, $-OC(O)N(R^{14})-$, $-CSN(R^{14})-$, $-N(R^{14})CO-$, $-N(R^{14})C(O)O-$, $-N(R^{14})CS-$, $-SON(R^{14})$, $-SO_2N(R^{14})$, $-N(R^{14})SO_2-$, $-N(R^{14})CON(R^{14})-$, $-N(R^{14})CSN(R^{14})-$, $-N(R^{14})SON(R^{14})-$ or $-N(R^{14})SO_2N(R^{14})$ group and R^{16} is a hydrogen atom or a group as just defined for R^{15}], $(-Alk^2)_pNHet^2$ (where $-NHet^2$ is an optionally substituted pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, morpholinyl, piperazinyl or thiomorpholinyl group), $-(Alk^2)_pOH$ or $-(Alk^2)_pAr$ (where Ar is a ntrogen-containing heteroaromatic group).

8. A compound according to Claim 7 wherein R^1 is a group $-Alk^2NH_2$, $-Alk^2NR^{15}R^{16}$, $-(Alk^2)_pNHet^2$ (where $-NHet^2$ is an optionally substituted pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or thiomorpholinyl group), $-Alk_2OH$ or $-Alk^2Ar$ (where Ar is an optionally substituted imidazolyl or benzimidazolyl group).

9. A compound of formula (1a):



(1a)

wherein R^1, R^2, R^3, R^4 and R^5 is each as defined in any one of Claim 1 to Claim 8.

10. A compound which is:
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-hydroxyethyl) phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[3-(2-hydroxyethyl) phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(1-imidazolyl) phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)-3-fluorophenyl]-5-chloro-*N*-[4-(2-hydroxyethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-(imidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(2-methylimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(2-isopropylimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-thiomorpholino)ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(tertbutylamino) ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4-methylpiperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4-ethylpiperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(3,5-dimethyl-piperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4-(pyrid-2-yl) piperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(pyrrolidin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(piperidin-1-yl)ethyl) phenyl]pyrimidine-2-amine;

and th salts, solvates, hydrates and N-oxides thereof.

11. A pharmaceutical composition comprising a compound according to any one of the preceding claims together with one or more pharmaceutically acceptable carriers, excipients or diluents.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/04043

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/42 C07D401/12 A61K31/505 A61P9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 958 935 A (PETER DAVID DAVIS) 28 September 1999 (1999-09-28) column 1 -column 10; claims	1-3,11
A	WO 99 01439 A (DU PONT) 14 January 1999 (1999-01-14) claims	1-3,11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
14 March 2001	23/03/2001

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/04043

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5958935 A	28-09-1999	AU 7631496 A	11-06-1997
		EP 0862560 A	09-09-1998
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		US 6103737 A	15-08-2000